Remarks

Claims 1-60 are currently pending in this application. Claims 1, 23, 34, 41-45, and 58 are amended. Claims 17, 18, 20, 30, 31, 33, 54, 55, and 57 are withdrawn from consideration as being drawn to non-elected inventions. Claims 45-47 and 56 are allowed. Claims 9, 15, 50, and 53 are objected to as being dependent on rejected claims, but are allowable if rewritten as independent claims.

1. Claim Rejections - 35 USC §112, first paragraph, Enablement

Claims 1-8, 10-14, 16, 19, 21-29, 32, 34-44, 48-49, 51-52, and 58-60 stand rejected under 35 USC §112, first paragraph as not enabled for an anti-IFN-γ light chain, an anti-IFN-γ heavy chain, an anti-IFN-γ antibody comprising less than all 6 CDRs (SEQ ID NOs: 34, 35, 36, 38, 41, and 43), anti-IFN-γ antibody less than 100% identical to SEQ ID NOs: 6, 8, 10, 12, 14, 16-22, and 30-33, anti-IFN-γ antibody comprising heavy and light chains of any given SEQ ID NOs: 6, 8, 10, 12, 14, 16-22, and 30-33 and fully human antibody to IFN-γ.

To satisfy the enablement requirement, an applicant must enable one of ordinary skill in the art to make and use the claimed invention. Enablement is decided with a view towards a weighing of the *Wands* factors, including (1) the quantity of experimentation required, (2) the amount of guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the skill of those in the art, (7) the predictability of the art, and (8)the breadth of the claims. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) However, enablement is not precluded by the necessity of even a considerable amount of experimentation in some cases, particularly if the experimentation is routine in nature, even when the art may be unpredictable. *U.S. v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988); *Ex Parte Mark*, 12 USPQ2d 1904(BPAI 1989); *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). Moreover, some unpredictability of the outcome of experimentation does not make the experimentation undue since an experiment would hardly be done if its outcome was known beforehand. *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976).

The Action asserts that there is insufficient guidance in the specification to enable one of skill in the art to make and use antibodies that comprise sequences at least 80% to 98% identical to the sequences recited in the claims. The Examiner has also raised the general issue of whether a claim limited only by sequences contained in either a heavy or a light chain variable region are sufficient to specify an antibody. As the Examiner has recognized, some claims, e.g., 9, 15, 45, 50, and 53, among others, include limitations directed at both the heavy and light chain variable regions. Other claims, e.g., 1, 23, and 34, among others, include limitations directed at only one variable region. As stated by the Examiner, "Janeway et al. (immunobiology, 6th Edition, 2004, Garland Science, p. 110-112) teach that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation are required in order to produce a protein having antigen binding function and that proper association of heavy and light chain variable regions is required in order to form functional binding sites." Office Action, page 4. As Applicants understand it, this issue forms part of the basis for the rejection of claims 1, 3-6, 10-12, 16, 17, 19, 22-26, 30, and 32-37. Please advise if this understanding is not correct.

While it may be true that both heavy and light chain variable regions are necessary for antigen binding in some cases, single variable regions capable of antigen binding can be selected. For example, US Patent No. 6,248,516 describes making and testing heavy chain variable regions for binding to an antigen. It was found that some heavy chain variable regions could bind to the antigen, in this case lysozyme, in the absence of a light chain. US Patent No. 6,248,516, Example 5, col. 24-26, Example 6, col. 26-27. This patent also predicts that similar results should be obtainable using light chain variable regions. US Patent No. 6,248,516, Example 11, col. 32. This patent also describes improving the binding affinity of a heavy chain variable region by mutagenesis of only amino acids within the CDR3 of a heavy chain variable region. US Patent No. 6,248,516, Example 7, col. 28-30. Further, it is known that some naturally-occurring antibodies contain heavy chains and lack light chains entirely. *See e.g.,* Desmyter et al. (2001), J. Biol. Chem. 276(28): 26285-90. Therefore, it has been demonstrated in the art that heavy chain variable regions can bind to an antigen in the absence of light chains, and similar results have been predicted for light chain variable regions. Further, it is known that alteration of only a heavy or a light chain CDR3 or both can alter the binding affinity of an antibody. *See e.g.* Schier et al. (1996),. J. Mol. Biol. 263: 551-67; Desiderio et al. (2001), J. Mol. Biol. 310: 603-15.

Further, it is known in the art that a heavy chain CDR3 can determine the binding specificity of an antibody. For example, human antibodies with binding specificity similar to that of a known murine antibody have been selected using a scheme in which the heavy chain CDR3 was the only sequence required to be retained. Klimka et al. (2000), British J. Cancer 83(2): 252-260. This selection produced antibodies, which had the binding specificity of the murine antibody, with sequences that diverged substantially from the murine heavy and light chain variable regions sequences, except at the heavy chain CDR3. Klimka et al., supra. Further, Ditzel et al. (J. Immunol. 157:739-49 (1996)) show that transplantation of only a heavy chain CDR3 from a polyreactive antibody to monospecific antibody transformed the monospecific antibody into a polyspecific antibody. Ditzel et al., at p.742-45, Fig.3. Moreover, Beiboer et al. (J. Mol. Biol. 296: 833-49 (2000)) succeeded in humanizing murine antibodies with a desired binding specificity using a "guided selection" procedure that required that the heavy chain CDR3 be retained and that the binding specificity of the antibody be maintained. They succeeded in finding an antibody having the original binding specificity, which retained the original heavy chain CDR3, but not the original light chain CDR3. Beiboer et al., supra. In addition, Barbas et al. (Proc. Natl. Acad. Sci. USA 92: 2529-33 (1995)) were able to transplant the heavy chain CDR3 from an antibody that bound to DNA into an unrelated antibody to generate an antibody that binds to DNA with an affinity very similar to that of the original antibody. Finally, Rader et al. (Proc. Natl. Acad. Sci. USA 95: 8910-15 (1998)) show that a humanization scheme that involves retaining only the heavy and light chain CDR3s rapidly generated antibodies with binding affinity and specificity similar to that of an original murine antibody. Therefore, these references indicate that a heavy chain CDR3, alone, can determine the binding specificity and affinity of an antibody of which it is a part. Thus, a claim directed to a heavy and/or a light chain CDR3 or variable region can have sufficient information to specify the portion of an antibody critical for binding. Thus, claims having limitations directed only to a heavy or light chain variable region or CDR3 are enabled.

The specification discloses that one of the light chain variable regions described (SEQ ID NO:12) and one of the heavy chain variable regions described (SEQ ID NO:14) can bind to IFN-γ with at least two different heavy or light chain variable region partners. All five antibodies disclosed in the application, *i.e.*, the 1118, 1118*, 1119, 1121, and 1121* antibodies, bind to IFN-γ. Specification, page 58, lines 20-24. The 1118 and 1118* antibodies have the same light chain variable regions (SEQ ID NO:12) but different heavy chain variable regions (SEQ ID NO: 10 and SEQ ID NO:30, respectively). Specification, Table 3, pages 60-61. Similarly, the 1121 and 1121* antibodies have the same heavy chain variable region (SEQ ID NO:14) but different light chain variable regions (SEQ ID NO:16 and SEQ ID NO:31, respectively). Specification, Table 3, pages 60-61. The light chain variable region of the 1121* antibody has a light chain CDR3 that bears little resemblance to the light chain CDR3 of the 1121 antibody. Specification, Figure 13. These data demonstrate that the binding of at least these two variable regions to IFN-γ does occur with more than one different light or heavy chain variable region binding partner. Given this information, claims in which the limitations are directed only to the heavy or light chain variable region are reasonable in scope.

Claims 4, 5, 7, 8, 10, 11, 13, 14, 23, 24, 27, 28, 34, 35, 38, 39, 48, 49, 51, and 52, (which are drawn to antibodies having a stated percent identity to a given sequence) have been rejected for lack of enablement. The Examiner states, "A person of skill in the art would not know which amino acids are essential, which amino acids are non-essential, and what particular lengths identify essential to binding to IFN-γ. There is insufficient guidance to direct a person of skill in the art to select particular amino acid is essential for antigen binding." Office Action, page 3.

Applicants assert that these claims are enabled for the following reasons. The art contains copious guidance to direct amino acid variation that can be made in antibody variable regions without affecting function. For example, an immunology textbook shows a chart depicting the pattern of variation of a human heavy chain variable region, which indicates that substantial variability occurs only within the CDRs. Hasemann and and Capra, Immunoglobulins: Structure and Function, Ch. 9 *in* Fundamental Immunology, Second Edition, Paul, ed., Raven Press, New York, 1989, pages 209-233, at 219. The CDRs are known to be major determinants in the antigen-combining site. Kabat *et al.* (1991), Sequences of Proteins of Immunological Interest, Vol. I, Public

Health Service N.I.H., Bethesda, MD, p. xv. Thus, one of skill in the art would be directed to vary sequences in the CDRs. Variations that do occur within framework regions are well defined because of the numerous known variable region sequences, alignments of which have been published. Kabat et al., *supra, at* pages 103-150 and 310-338; V Base, *available at* http://vbase.mrc-cpe.cam.ac.uk/alignments2.php (visited 12/21/05). For example, among human VH region sequences, residues 1-3 of the first framework region vary occasionally, but within a very limited range of amino acids, whereas the leucine at position 4 is almost invariant. Kabat et al., *supra, at* 310-338. Thus, one of skill in the art would be informed that a limited range of variations at positions 1-3 of the first framework region of the heavy chain variable region would likely not affect antigen binding by the antibody, whereas variation at position 4 would possibly not leave the activity of the antibody unchanged. Similarly, human light chain kappa variable region sequences vary within a limited range of amino acids at positions 1-4 of the first framework region and have an almost invariant threonine at position 5. Kabat et al., *supra, at* 103-150. Thus, one of skill in the art would be guided not to vary the threonine at position 5 and to vary the amino acids at positions 1-4 only within a limited range. Similar considerations can be applied throughout the heavy and light chain variable region framework segments to determine what variations at what positions are likely to be permissible without affecting antigen binding. Thus, published sequence alignments are adequate to guide variations within framework regions, and testing the resulting antibodies for binding could confirm the activity of altered antibodies. With respect to variation within CDRs, since these regions are known to be important for antigen binding, alterations can be assessed for effects on antigen binding using, for example, an ELISA assay, an assay well-known in the art. Specification, page 58, lines 20-24. Further, it is known in the art how to make amino acid changes to a known sequence. *See e.g.,* Desiderio et al., *supra;* Schier et al., *supra.* Thus, one of skill in the art would have copious guidance both in selecting which amino acids to alter and in selecting how to alter them. Therefore, claims 4, 5, 7, 8, 10, 11, 13, 14, 23, 24, 27, 28, 34, 35, 38, 39, 48, 49, 51, and 52 are enabled.

Claims 1 and 2 are of moderate breadth, and claim 1 is supported by two disclosed species within the scope of part (a). Claim 1 encompasses antibodies that comprise a heavy chain CDR3 comprising at least 7 of the amino acids of SEQ ID NO:36

in the same order and spacing as they occur in SEQ ID NO:36, and and claim 2 encompasses antibodies of claim 1 that further comprise a light chain CDR3 comprising at least 8 of the amino acids of SEQ ID NO:43 in the same order and spacing as they occur in SEQ ID NO:43 or comprising at least 9 of the amino acids of SEQ ID NO:44 in the same order and spacing as they occur in SEQ ID NO:44. Since SEQ ID NOs:36, 43, and 44 have only 8, 9 and 10 amino acids, respectively, claims 1 and 2 allow a substitution of only one amino acid in each of these sequences. SEQ ID NOS: 36 and 37 differ by only one amino acid. Therefore, SEQ ID NO:37 and SEQ ID NO:36 are two species within the scope of part (a) of claim 1. Thus, the scope of claims 1 and 2 is moderate.

One of skill in the art will expect that an antibody comprising the CDR3s of claims 1 and 2 will bind IFN-γ, since it is recognized in the art that CDR3 regions of the heavy and light chains, particularly the heavy chain CDR3, are the major determinants of antigen binding (as discussed, for example, on). *See e.g.* Page 38, lines 7-9 of the specification; Desmyter et al. (2001), J. Biol. Chem. 276(28): 26285-90; Schier et al. (1996), J. Mol. Biol. 263: 551-67; Desiderio et al. (2001), J. Mol. Biol. 310: 603-15; Kabat *et al. supra*; Xu and Davis (2000), Immunity 13: 37-45. For example, in Schier et al. (*supra),* a collection of antibodies is described that differ from the starting antibody by one or more amino acids within the heavy or light chain CDR3 and bind to the same antigen as the starting antibody, but with higher affinity. Moreover, Schier et al. and Desiderio et al. (*supra)*, among many others, describe the construction of antibodies with altered sequences. Xu and Davis state, "We would suggest that uniform CDR shapes are important for the stability of a binding site, with the exception of V_H CDR3, which has to "fit" the antigen surface much more precisely. . . .The data presented here, as well as previous work, strongly suggest that the purpose of highly diverse CDR3 regions in all antigen receptors is to provide antigen specificity.". Binding assays to determine if the antibodies can bind IFN-γ are described in the specification in Example 2. Therefore, information known in the art plus the as-filed specification provide considerable direction and guidance for making antibodies of the invention, whose sequences differ from disclosed CDR sequences by only one amino acid.The Action also invites Applicant to amend the claims to recite "specifically binds to IFN-γ" instead of "the antibody can bind specifically to IFN-γ." Applicants have amended the claims accordingly, thus obviating rejection on this basis.

Under *Wands,* claims 1-8, 10-14, 16, 19, 21-29, 32, 34-44, 48-49, 51-52, and 58-60 are enabled. First, only a moderate amount of routine experimentation would be required to find other species within the scope of these claims, and guidance for such experimentation is included in the specification and known in the art, as explained above. Second, a number of working examples of antibodies that bind to IFN-γ are included in the specification, i.e., 1118, 1118*, 1119, 1121, and 1121*, which together comprise four different heavy and light chains comprising two different light chain CDR3 sequences (which differ at all but two positions) and two different heavy chain CDR3 sequences (which differ at one position). *See* Figures 12 and 13. Fourth, the invention is an antibody, and there is a vast amount of sequence, structural, and functional information available in the art for antibodies, as a class. *See e.g.,* Kabat *et al.* (1991), Sequences of Proteins of Immunological Interest, Public Health Service N.I.H., Bethesda, MD. Moreover, antibodies have a special position in the realm of biotechnology arts because the USPTO has acknowledged that the art of making antibodies is mature and well developed, a position that has been sanctioned by the courts. *Noelle v. Lederman,* 69 USPQ2d 1508, 1513-1514 (Fed. Cir. 2004), *citing* Synopsis of Application Written Description Guidelines, at 60, available at *http://www.uspto.gov/web/menu/written.pdf*. Thus, the art of making antibodies is considered more predictable than other areas of biotechnology. Further, the skill of practicioners in biotechnology is high. Finally, the claims are of moderate breadth. Therefore, Applicants submit that all claims are enabled.

2. Claim Rejections - 35 USC §112, first paragraph—Written Description

Claims 1-8, 10-14, 16, 19, 21-29, 32, 34-40, 48-49, 51-52, and 58-60 stand rejected under 35 USC §112, first paragraph for failing to comply with the written description requirement. The Action asserts that Applicant is not in possession of an anti-IFN-γ light chain, an anti-IFN-γ heavy chain, an anti-IFN-γ antibody comprising less than all 6 CDRs (SEQ ID NOs: 34, 35, 36, 38, 41, and 43), anti-IFN-γ antibody less than 100% identical to SEQ ID NOs: 6, 8, 10, 12, 14, 16-22, and 30-33, anti-IFN-γ antibody comprising heavy and light chains of any given SEQ ID NOs: 6, 8, 10, 12, 14, 16-22, and

30-33 and fully human antibody to IFN-γ. The Action further asserts that a representative description of the structural and functional properties of the claimed invention is needed to satisfy the written description requirement.

To satisfy the written description requirement an applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*" *Vas Cath v. Mahurkar,* 19 USPQ2d 1111 (Fed. Cir. 1991). Generally, what must be described is a "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Enzo v. Gen-Probe*, 3 USPQ2d 1609 (Fed. Cir. 2002). "It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement." *Enzo, supra.* Further, the description of a genus may be adequate when only one species within the genus is disclosed, particularly in predictable arts. *Bilstad v. Wakalopulos,* 386 F.3d 1116, 1124-1126, 72, USPQ2d 1785 (Fed. Cir. 2004). As stated above, the art of making antibodies has been recognized as a mature, and thus relatively predictable, art, *Noelle v. Lederman,* 69 USPQ2d 1508 (Fed. Cir. 2004). In less predictable arts, description of more species within a claimed genus can be necessary to show possession of the genus. *Bilstad,* at 1125.

In keeping with this guidance, Example 14 of the Written Description Guidelines indicates that variants of a protein are adequately described where the specification indicates that the variant has a certain percentage identity to a particular protein sequence, wherein the variant retains the activity of the unchanged protein, and wherein the specification demonstrates the activity of the unchanged protein, thereby providing an assay for identifying the variants with the claimed activity.

In the instant specification, Applicants have demonstrated actual possession of plural species within the scope of individual subparts of the rejected claims, *i.e.*, antibodies 1118, 1118*, 1119, 1121, and 1121*. For example, subpart (a) of claim 23 claims an antibody comprising a sequence at least 96% identical to SEQ ID NO:6. The percent identity between the 1118 and 1119 heavy chain variable regions (SEQ ID NOS:10 and 6, respectively) is about 97.4.6% and that between the 1119 and 1121 variable regions (SEQ ID NOS:6 and 14, respectively) and the 1118* and 1119 variable regions (SEQ ID NOS:30 and 6, respectively) are about 99.1% and 96.6%, respectively. Thus, the 1118, 1118*, 1121, and 1119 heavy chain variable regions all fall within the scope of subpart (a) of claim 1. Such comparisons show that each subpart of claim 23 is supported by plural species within it. Similarly, the percent identities between the 1118 and 1119 (SEQ ID NOS:12 and 8), the 1118 and 1121*(SEQ ID NOS:12 and 31), and the 1118 and 1121 (SEQ ID NOS:12 and 16) light chain variable regions are, respectively, about 99%, 87%, and 99%. Therefore, the SEQ ID NOS:8, 12, and 16 all fall within the scope of subpart (b) of claim 34. Thus, all subparts of claim 34, with the exception of subpart (d), are supported by plural species. Therefore, the disclosure includes multiple species within the scope of individual subparts, i.e., (a), (b), etc., of, for example, claims 23, 24, 27, 34 and 35, and also species that bind to IFN-γ that are outside the percent identity specified by some of the claims. The disclosure of multiple species within the scope of the claims strengthens the written description.

In the instant application, a number of claims encompass antibodies that have a given percent identity to disclosed sequences while retaining the ability to bind IFN-γ. Other claims (such as, for example, claims 1 and 2) encompass antibodies that can bind to IFN-γ comprising one or more CDRs with at least a given number of the amino acids in a given sequence in the same order and spacing as they occur in that sequence. The specification provides an assay that will identify these antibodies. As discussed above, the art of making antibodies is considered to be more mature, i.e., more predictable, than some other areas of biotechnology. Consequently, the disclosure of plural species within the scope of many of the rejected claims, along with the predictable nature of the art, would lead one of skill in the art to conclude that Applicants were in possession of the common attributes of the claimed antibodies. Therefore, Applicants submit that the claims satisfy the written description requirement, and respectfully request that this ground of rejection be withdrawn.

3. Claim Rejections - 35 USC §102

Claim 41 stands rejected under 35 USC §102(b) as being anticipated by US Patent No. 6,075,181 (the '181 patent). Specifically, the Action states that the '181 patent teaches fully human IFN-γ antibodies, which would inherently inhibit activity of human and chimpanzee IFN-γ without inhibiting activity of murine and monkey IFN-γ. As stated in MPEP §2131, a claim is anticipated only if each and every element as set forth in the claim is described, either expressly or inherently, in a single prior art reference. Applicants submit that the antibodies of amended claim 41 are not taught in the '181 patent because the '181 patent does not describe an antibody that cannot inhibit the biological activity of a mutated version of human IFN-γ in which the histidine at position 19 has been replaced with aspartate and/or in which the serine at position 20 has been replaced with a proline. Similarly, the '181 patent does not disclose IFN-γ antibodies as recited in amended claim 43, that can inhibit the biological activity of human, but not of cynomolgus monkey, IFN-γ and can inhibit the activity of a mutated version of cynomolgus monkey IFN-γ that comprises a histidine at position 19 in place of aspartate, a serine at position 20 in place of proline, and a serine at position 65 in place of arginine. The '181 patent does not describe the making of any anti-IFN-γ antibodies, but merely lists IFN-γ as a potential antigen that could be used to generate antibodies in xenomice. In addition, the antibodies of claim 41 are not inherently described in the '181 patent, since the '181 patent does not teach or suggest that antibodies can be generated that specifically inhibit IFN-γ in humans and chimpanzees without being able to inhibit cynomolgus monkey IFN-γ and murine IFN-γ. Therefore, the '181 patent does not anticipate claims 41-44, and Applicants respectfully request that rejection on this basis be withdrawn.

4. Claim Rejections - 35 USC §103

Claims 41-44 stand rejected under 35 USC §103(a) as obvious over US Patent No. 6,075,181 (the '181 patent) in view of Thakur *et al.* (Molecular Immunology, 1999, vol. 36:1107-1115). To establish a *prima facie* case of obviousness, the cited references must teach or suggest every claim limitation. MPEP § 2143. As discussed above, claims 41 and 43 each contain limitations not found in the '181 patent. As explained below, Thakur et al. does not supply the missing limitations. With respect to Thakur et al., Applicants point out that cynomolgus monkey IFN-γ (the sequence of which can be found in NCBI BAA14050, which is attached) and the rhesus monkey IFN-γ sequence disclosed in Thakur et al. are identical. *See* attached alignment. Thakur et al. show that residues 19 and 20, which are different in human and rhesus IFN-γ, are not important for the inhibition of IFN-γ activity by their murine anti- IFN-γ antibody. Tables 1 and 2, page 1112 and accompanying text. Therefore, the antibody of Thakur et al. is different from the antibodies disclosed in the instant application because residues 19 and 20 of IFN-γ are critical for the inhibition of IFN-γ activity by at least one of the disclosed antibodies. Specification, Examples 7 and 8. Since amended claims 41 and 43 contain limitations that are directed at the importance of these residues for inhibition if IFN-γ activity, these claims are both novel and nonobvious over the combination of Thakur and the '181 patent.

CONCLUSION

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended or as originally presented. Allowance of the claims is thereby respectfully solicited.

If there are any questions or comments regarding this Response or application, the Examiner is encouraged to contact the undersigned representative as indicated below at 312-913-0001.

Respectfully submitted,
McDonnell Boehnen Hulbert & Berghoff LLP

Date: January 26, 2006

By: Jason J. Derry
Reg. No. 50,692

Phone: 312-913-0001
Fax: 312-913-0002

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Gap Results

Refine

```
 GAP of: 1118_HC_Var_REg  check: 8051  from: 1  to: 117

A838

 to: 1119_HC_Var_Reg  check: 6629  from: 1  to: 117

a838

 Symbol comparison table: blosum62.cmp CompCheck: 1102
BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid
           substitution matrices from protein blocks.  Proc. Natl. Acad.
           Sci. USA 89: 10915-10919.

        Gap Weight:     12      Average Match:  2.778
     Length Weight:      4   Average Mismatch: -2.248

           Quality:    607             Length:    117
             Ratio:  5.188               Gaps:      0
 Percent Similarity: 97.436   Percent Identity: 97.436

        Match display thresholds for the alignment(s):
                    | = IDENTITY
                    : =   2
                    . =   1

 1118_HC_Var_REg x 1119_HC_Var_Reg January 5, 2006 11:45  ..

               .         .         .         .         .
    1 EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGI 50
      |||||||||||||||||||||||||||.|||||||||||||||||| |||
    1 EVQLVQSGAEVKKPGESLKISCKGSGYNFTSYWIGWVRQMPGKGLELMGI 50
               .         .         .         .         .
   51 IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCGSGS 100
      ||||||||||||||||||||||||||||||||||||||||||||||||||
   51 IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCGSGS 100
               .
  101 YWYFDLWGRGTLVTVSS 117
      |.|||||||||||||||
  101 YFYFDLWGRGTLVTVSS 117
```

Input Sequence: 1118_HC_Var_REg

Gap Results

Refine

```
 GAP of: 1119_HC_Var_Reg  check: 6629  from: 1  to: 117

a838

 to: 1121_HC_Var_REg  check: 7394  from: 1  to: 117

A838

 Symbol comparison table: blosum62.cmp CompCheck: 1102
BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid
           substitution matrices from protein blocks.  Proc. Natl. Acad.
           Sci. USA 89: 10915-10919.

        Gap Weight:      12      Average Match:  2.778
     Length Weight:       4   Average Mismatch: -2.248

           Quality:     618            Length:    117
             Ratio:   5.282              Gaps:      0
 Percent Similarity: 99.145   Percent Identity: 99.145

       Match display thresholds for the alignment(s):
                   | = IDENTITY
                   : =   2
                   . =   1

 1119_HC_Var_Reg x 1121_HC_Var_REg January 5, 2006 11:40  ..

                         .         .         .         .         .
       1 EVQLVQSGAEVKKPGESLKISCKGSGYNFTSYWIGWVRQMPGKGLELMGI 50
         ||||||||||||||||||||||||||||||||||||||||||||||||||
       1 EVQLVQSGAEVKKPGESLKISCKGSGYNFTSYWIGWVRQMPGKGLELMGI 50
                  .         .         .         .         .
      51 IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCGSGS 100
         ||||||||||||||||||||||||||||||||||||||||||||||||||
      51 IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCGSGS 100
                  .
     101 YFYFDLWGRGTLVTVSS 117
         |.|||||||||||||||
     101 YWYFDLWGRGTLVTVSS 117
```

Input Sequence: 1119_HC_Var_Reg

Gap Results

Refine

```
 GAP of: 1118_HC_Var_Reg  check: 7801  from: 1  to: 117

A838

 to: 1119_HC_Var_Reg  check: 6629  from: 1  to: 117

a838

 Symbol comparison table: blosum62.cmp CompCheck: 1102
BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid
           substitution matrices from protein blocks.  Proc. Natl. Acad.
           Sci. USA 89: 10915-10919.

        Gap Weight:      12      Average Match:  2.778
     Length Weight:       4   Average Mismatch: -2.248

           Quality:     593            Length:    117
             Ratio:   5.068              Gaps:      0
 Percent Similarity: 96.581   Percent Identity: 96.581

       Match display thresholds for the alignment(s):
                   | = IDENTITY
                   : =   2
                   . =   1

 1118_HC_Var_Reg x 1119_HC_Var_Reg January 5, 2006 11:43  ..

                 .         .         .         .         .
      1 EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIGWVRQMPGKGLEWMGI 50
        |||||||||||||||||||||||||||.|||||||||||||||||| |||
      1 EVQLVQSGAEVKKPGESLKISCKGSGYNFTSYWIGWVRQMPGKGLELMGI 50

                 .         .         .         .         .
     51 IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCGSGS 100
        ||||||||||||||||||||||||||||||||||||||||||||||||||
     51 IYPGDSDTRYSPSFQGQVTISADKSISTAYLQWSSLKASDTAMYYCGSGS 100

                 .
    101 YWYFDLRGRGTLVTVSS 117
        |.|||| ||||||||||
    101 YFYFDLWGRGTLVTVSS 117
```

Input Sequence: 1118_HC_Var_Reg

Gap Results

Refine

```
 GAP of: 1118_LC_Var._Reg.  check: 613  from: 1  to: 108

A838

 to: 1119_LC_Var._Reg  check: 811  from: 1  to: 108

A838

 Symbol comparison table: blosum62.cmp CompCheck: 1102
BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid
           substitution matrices from protein blocks.  Proc. Natl. Acad.
           Sci. USA 89: 10915-10919.

        Gap Weight:      12      Average Match:  2.778
     Length Weight:       4   Average Mismatch: -2.248

           Quality:     547             Length:    108
             Ratio:   5.065               Gaps:      0
 Percent Similarity:  99.074   Percent Identity: 99.074

       Match display thresholds for the alignment(s):
                   | = IDENTITY
                   : =   2
                   . =   1

 1118_LC_Var._Reg. x 1119_LC_Var._Reg December 14, 2005 15:21  ..

                  .         .         .         .         .
       1 EIVLTQSPGTLSLSPGERATLSCRASQSVSSSSLAWYQQKPGQAPRLLIY 50
         ||||||||||||||||||||||||||||||||| ||||||||||||||||
       1 EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY 50
                  .         .         .         .         .
      51 GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQRSGGSSFTFG 100
         ||||||||||||||||||||||||||||||||||||||||||||||||||
      51 GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQRSGGSSFTFG 100

     101 PGTKVDIK 108
         ||||||||
     101 PGTKVDIK 108
```

Input Sequence: 1118_LC_Var._Reg.

Gap Results

Refine

```
 GAP of: 1118_LC_Var._Reg.  check: 613  from: 1  to: 108

A838

 to: 1121_LC_var_Reg.  check: 6381  from: 1  to: 109

A838

 Symbol comparison table: blosum62.cmp CompCheck: 1102
BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid
           substitution matrices from protein blocks.  Proc. Natl. Acad.
           Sci. USA 89: 10915-10919.

        Gap Weight:     12      Average Match:  2.778
     Length Weight:      4   Average Mismatch: -2.248

           Quality:    474             Length:    109
             Ratio:  4.389               Gaps:      1
 Percent Similarity: 89.815   Percent Identity: 87.037

       Match display thresholds for the alignment(s):
                   | = IDENTITY
                   : =   2
                   . =   1

 1118_LC_Var._Reg. x 1121_LC_var_Reg. January 5, 2006 12:00  ..

                         .         .         .         .         .
       1 EIVLTQSPGTLSLSPGERATLSCRASQSVSSSSLAWYQQKPGQAPRLLIY 50
         ||||||||||||||||||||||||||||: || |||||||||| ||||||
       1 EIVLTQSPGTLSLSPGERATLSCRASQSIISSYLAWYQQKPGQTPRLLIY 50
                         .         .         .         .         .
      51 GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQRSGGS.SFTF 99
         | ||||||||||||||||||||||||.|||||||||||||. | |  :||
      51 GVSSRATGIPDRFSGSGSGTDFTLTITRLEPEDFAVYYCQQYGNSFMYTF 100

     100 GPGTKVDIK 108
         | |||.:||
     101 GQGTKLEIK 109
```

Input Sequence: 1118_LC_Var._Reg.

Gap Results

Refine

```
 GAP of: 1118_LC_Var._Reg.  check: 613  from: 1  to: 108

A838

 to: 1121_LC_Var_Reg  check: 811  from: 1  to: 108

A838

 Symbol comparison table: blosum62.cmp CompCheck: 1102
BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid
           substitution matrices from protein blocks.  Proc. Natl. Acad.
           Sci. USA 89: 10915-10919.

        Gap Weight:     12       Average Match:  2.778
     Length Weight:      4    Average Mismatch: -2.248

           Quality:    547              Length:    108
             Ratio:  5.065                Gaps:      0
 Percent Similarity: 99.074   Percent Identity: 99.074

       Match display thresholds for the alignment(s):
                   | = IDENTITY
                   : =   2
                   . =   1

 1118_LC_Var._Reg. x 1121_LC_Var_Reg December 14, 2005 15:22  ..

                 .         .         .         .         .
      1 EIVLTQSPGTLSLSPGERATLSCRASQSVSSSSLAWYQQKPGQAPRLLIY 50
        |||||||||||||||||||||||||||||||| |||||||||||||||||
      1 EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIY 50
                 .         .         .         .         .
     51 GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQRSGGSSFTFG 100
        ||||||||||||||||||||||||||||||||||||||||||||||||||
     51 GASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQRSGGSSFTFG 100

    101 PGTKVDIK 108
        ||||||||
    101 PGTKVDIK 108
```

Input Sequence: 1118_LC_Var._Reg.

Gap Results

Refine

```
 GAP of: cyno_ifn_gamma  check: 602  from: 1  to: 165

BAA14050

 to: rhesus_IFN_gamma  check: 4024  from: 1  to: 142

Thakur et al. (2000), Molec. Immunol. 36: 1107-15
WPDEF Thakur et al. (2000), Molec. Immunol. 36: 1107-15

 Symbol comparison table: blosum62.cmp CompCheck: 1102
BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid
           substitution matrices from protein blocks.  Proc. Natl. Acad.
           Sci. USA 89: 10915-10919.

         Gap Weight:     12      Average Match:  2.778
      Length Weight:      4   Average Mismatch: -2.248

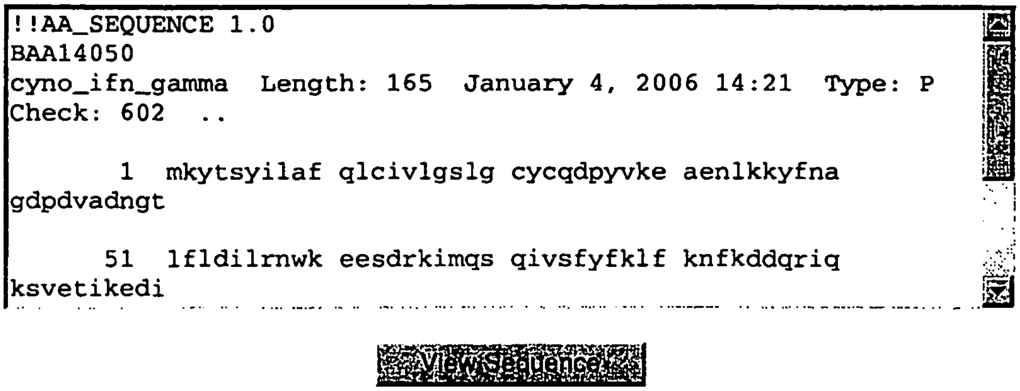
            Quality:    726             Length:    165
              Ratio:  5.113               Gaps:      0
 Percent Similarity: 100.000   Percent Identity: 100.000

       Match display thresholds for the alignment(s):
                    | = IDENTITY
                    : =   2
                    . =   1

 cyno_ifn_gamma x rhesus_IFN_gamma January 13, 2006 15:22  ..

                  .         .         .         .         .
       1 mkytsyilafqlcivlgslgcycqdpyvkeaenlkkyfnagdpdvadngt 50
                                |||||||||||||||||||||||||||
       1 .......................qdpyvkeaenlkkyfnagdpdvadngt 27
                  .         .         .         .         .
      51 lfldilrnwkeesdrkimqsqivsfyfklfknfkddqriqksvetikedi 100
         ||||||||||||||||||||||||||||||||||||||||||||||||||
      28 lfldilrnwkeesdrkimqsqivsfyfklfknfkddqriqksvetikedi 77
                  .         .         .         .         .
     101 nvkffnsnkkkrddfekltnysvtdsnvqrkavheliqvmaelspaakig 150
         ||||||||||||||||||||||||||||||||||||||||||||||||||
      78 nvkffnsnkkkrddfekltnysvtdsnvqrkavheliqvmaelspaakig 127
                  .
     151 krkrsqmfrgrrasq 165
         |||||||||||||||
     128 krkrsqmfrgrrasq 142
```

Input Sequence: cyno_ifn_gamma

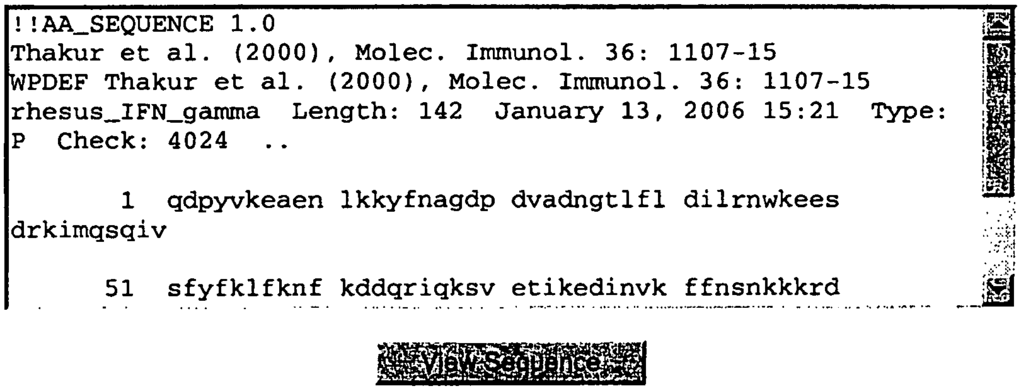


```
!!AA_SEQUENCE 1.0
BAA14050
cyno_ifn_gamma  Length: 165  January 4, 2006 14:21  Type: P
Check: 602  ..

       1  mkytsyilaf qlcivlgslg cycqdpyvke aenlkkyfna
gdpdvadngt

      51  lfldilrnwk eesdrkimqs qivsfyfklf knfkddqriq
ksvetikedi
```

Input Sequence: rhesus_IFN_gamma



```
!!AA_SEQUENCE 1.0
Thakur et al. (2000), Molec. Immunol. 36: 1107-15
WPDEF Thakur et al. (2000), Molec. Immunol. 36: 1107-15
rhesus_IFN_gamma  Length: 142  January 13, 2006 15:21  Type:
P  Check: 4024  ..

       1  qdpyvkeaen lkkyfnagdp dvadngtlfl dilrnwkees
drkimqsqiv

      51  sfyfklfknf kddqriqksv etikedinvk ffnsnkkkrd
```

Protein

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Range: from begin to end Features: ☐ SNP ☐ CDD ☑ MGC ☑ HPRD ☑ STS ☑ tRNA

☐ 1: BAA14050. Reports interferon-gamma ...[gi:1754524]

BLink, Conserved Domains, Links

```
LOCUS       BAA14050                 165 aa            linear   PRI 08-MAY-1999
DEFINITION  interferon-gamma [Macaca fascicularis].
ACCESSION   BAA14050
VERSION     BAA14050.1  GI:1754524
DBSOURCE    accession D89985.1
KEYWORDS    .
SOURCE      Macaca fascicularis (crab-eating macaque)
  ORGANISM  Macaca fascicularis
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Primates; Catarrhini;
            Cercopithecidae; Cercopithecinae; Macaca.
REFERENCE   1  (sites)
  AUTHORS   Tatsumi,M. and Sata,T.
  TITLE     Molecular cloning and expression of cynomolgus monkey
            interferon-gamma cDNA
  JOURNAL   Int. Arch. Allergy Immunol. 114 (3), 229-236 (1997)
   PUBMED   9363903
REFERENCE   2  (residues 1 to 165)
  AUTHORS   Tatsumi,M.
  TITLE     Direct Submission
  JOURNAL   Submitted (20-DEC-1996) Masashi Tatsumi, National Institute of
            Health, Department of Veterinary Science; 1-23-1 Toyama,
            Shinjuku-ku, Tokyo 162, Japan (E-mail:tatsu@nih.go.jp,
            Tel:+81-3-5285-1111, Fax:+81-3-5285-1179)
FEATURES             Location/Qualifiers
     source          1..165
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                     /db_xref="taxon:9541"
                     /cell_type="PBMC"
     Protein         1..165
                     /product="interferon-gamma"
     CDS             1..165
                     /gene="IFN-gamma"
                     /coded_by="D89985.1:1..498"
ORIGIN
        1 mkytsyilaf qlcivlgslg cycqdpyvke aenlkkyfna gdpdvadngt lfldilrnwk
       61 eesdrkimqs qivsfyfklf knfkddqriq ksvetikedi nvkffnsnkk krddfekltn
      121 ysvtdsnvqr kavheliqvm aelspaakig krkrsqmfrg rrasq
//
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